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(54) **A superior tasting pharmaceutical composition having porous particles and the process of preparing such pharmaceutical composition.**

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Descripti n

A superi r tasting pharmaceutical composition having porous particles and the novel process for preparing said pharmaceutical composition is disclosed herein. The improved pharmaceutical composition is especially well suited for preparing pharmaceutical compositions of antacids such as aluminum hydroxide and magnesium hydroxide which typically have a chalky and gritty taste and are therefore unpleasant to administer orally. The prior art describes the use of fluid bed granulators that produce porous granules. In this novel approach, effervescence-producing ingredients are used for preparing porous granules.

The process described in further detail below can be summarized as follows. Stoichiometric amounts of an appropriate base and an appropriate acid are mixed and compressed in a press to form a compact. The compact is then milled to form an evenly distributed stoichiometric mixture of the base and the acid. A pharmacologically active agent is then added to the mixture to form an active mixture that is then granulated in admixture with an appropriate amount of a granulating agent, such appropriate amount being well-known in the art, wherein the granulating agent in combination with the active mixture forms a wet granulation having minimal water activity. The wet granulated material is then dried whereby the applied heat and the water cause the acid and the base to react releasing gas from the wet granulation to form porous particles. The porous particles are then milled to form a powder which can be compressed to form a tablet suitable for oral administration.

It is important to note that the essential feature of the present invention is the production of a pharmaceutical composition of porous particles incorporating the pharmacologically active agent. In this respect, therefore, the exact order of the steps in producing such porous particles is unimportant.

For example, the approximately stoichiometric amounts of an appropriate acid and an appropriate base can be milled separately and then mixed to form the effervescent mixture. The effervescent mixture is then added to a preparation of a pharmacologically active agent to form an active mixture. The active mixture is then granulated in admixture with an appropriate amount of a granulating agent, such appropriate amount being well-known in the art, to form a wet granulation containing water. The wet granulation is then dried with applied heat such that the applied heat and the water in the wet granulation cause the acid and the base to react releasing gas from the wet granulation to form porous particles. The porous particles can then be milled to form a powder, which can be compressed to form a tablet, used in a reconstitutable powder dosage form or filled in a capsule as a quick dissolving powder.

Likewise, the stoichiometric amounts of an appropriate acid and an appropriate base can be mixed to form a mixture of the appropriate acid and the appropriate base. The mixture of the appropriate acid and the appropriate base is then granulated with an appropriate amount of a non-aqueous granulating liquid containing a binding agent dissolved in absolute alcohol to produce a wet granulation. The wet granulation is then dried to form granules of the mixture of the appropriate acid and the appropriate base, which are then milled to form an effervescent mixture of fine particle size. The effervescent mixture of fine particle size is then added to a preparation of a pharmacologically active agent to form an active mixture. The active mixture is then granulated in admixture with an appropriate amount of a granulating agent, such appropriate amount being well-known in the art, to form a wet granulation containing water. The wet granulation is then dried with applied heat such that the applied heat and the water cause the acid and the base to effervesce, forming porous particles. The porous particles can then be milled to form a powder, which can be compressed to form a tablet, used in a reconstitutable powder dosage form or filled in a capsule as a quick dissolving powder.

A preferred embodiment of the invention is where the active ingredient is an antacid such as aluminum hydroxide or magnesium hydroxide or a combination thereof or such combination in combination with other antacids. A more preferred embodiment of the invention is where the acid is citric acid, tartaric acid, malic acid or maleic acid and the base is sodium or potassium bicarbonate or sodium or potassium carbonate. Other preferred embodiments include compositions in which the active agent is a calcium supplement, such as calcium carbonate, or a reconstitutable powder having methylcellulose, hydroxypropylcellulose or other similar agents as the active agent.

The present invention is directed towards a process for producing a superior tasting pharmaceutical composition having porous granules produced through in situ gas generation using effervescence-producing ingr dients. Th process is useful for preparing pharmaceutical compositions having active ingredients that are hydrophobic by nature and that have a chalky and/or gritty taste such as antacids and calcium supplements. Th composition may also prove useful in the delivery of pharmacological agents such as terfenadine as well.

The use of high shear mixers in wet granulation can produce hard granules with low porosity. A commercially available proc ss claims to produce antacid tabl ts with a less gritty taste using porous

granulations made in a fluid bed granulator. This novel, yet simple, approach involves the use of effervescence-producing ingredients for preparing pharmaceutical compositions having porous calcium carbonate granules as well as compositions having porous magaldrate granules. It will be appreciated that other formulations including aluminum hydroxide and magnesium hydroxide, as well as various combinations thereof, are also encompassed within the scope of the invention, as well as other pharmaceutically active agents.

Calcium carbonate was granulated in a laboratory high shear mixer using 10% W/W pregelatinized starch as the binder, water or simple syrup as the granulating liquid, and an effervescent mixture of sodium bicarbonate and citric acid for in situ gas generation during the process to increase the granule porosity. Compacts of a stoichiometric mixture of sodium bicarbonate and citric acid were prepared using a hydraulic press. It will be understood that other mixtures of acids and bases could also be used in this process, including sodium carbonate, potassium bicarbonate, potassium carbonate, tartaric acid, malic acid, maleic acid, etc. It will be recognized that this list is not exhaustive and that other acids and bases are encompassed within the scope of the invention as well.

The compacts were ground and used at 1.76% and 3.52% W/W levels in the preparation of calcium carbonate granulations. A calcium carbonate granulation prepared without the effervescent mixture was used as the control. The bulk and tap density, and the mercury intrusion porosimetry data on the individual cuts showed the granules prepared using this approach have greater porosity than the control granules. The -40 + 60 and -60 + 80 sieve cuts of the porous and control granules were compressed on a hydraulic press. A taste test was conducted which showed that the granules prepared using this approach and the tablets made therefrom were less gritty than the control samples and tended to dissolve in the mouth giving a superior taste and mouth feel.

This novel, yet simple approach was also used to prepare porous mannitol granules. Mannitol granulations were prepared in a laboratory high shear mixer using 10% W/W pregelatinized starch as the binder, water as the granulating liquid, and an effervescent combination of sodium bicarbonate and citric acid for in situ gas generation during the process to increase the granule porosity. A stoichiometric mixture of sodium bicarbonate and citric acid was first compressed on a hydraulic press and the compacts were ground and used at 1.76%, 2.64%, 3.52%, and 4.40% W/W levels in the preparation of mannitol granulations. Several process conditions were tried for maximizing the granule porosity. Control mannitol granulations were also prepared in a fluid bed granulator using the same formula and process but without the effervescent mixture. The bulk and tap densities of the various sieve cuts of these granulations were measured. Similarly, the porosity of the individual sieve cuts was measured using a mercury intrusion porosimeter. The results of this comparison indicate that the porosity of mannitol granules could be increased through in situ gas generation using effervescence-producing ingredients under controlled granulating conditions.

In another approach to testing the efficacy of increasing granule porosity through in situ gas generation using effervescence-producing ingredients, mannitol, sodium bicarbonate, anhydrous citric acid, pregelatinized starch and hydroxypropyl methylcellulose (HPMC) were used. The granulations were prepared in a high shear mixer and dried in an oven at 54 °C (130 °F). In an attempt to increase the granule porosity efforts were made to minimize the amount of the effervescent reaction taking place during the agglomeration process and thus concentrating the majority of the effervescent reaction in the drying step. In order to minimize the effervescent reaction during the agglomeration process, two approaches were tried. The first approach used a dispersion of hydroxypropyl methylcellulose in water or isopropanol instead of the plain deionized water. The second approach used a refrigerated powder blend and cold (10 °C) water as the granulating liquid. To investigate the effect of the effervescent-mixture concentration on granule porosity, granulations containing 1.76%, 2.64%, 3.52% and 4.40% w/w levels of the effervescent mixture were prepared. Control granulations of mannitol without the effervescent mixture were also prepared for comparison. The +16, -16 + 20, -20 + 40, -40 + 60, -60 + 80 and -80/pan sieve cuts of the dried granulations were separated using a sieve shaker. The bulk and tap density of the individual sieve cuts was also measured. Similarly, the porosity of the individual sieve cuts was also measured using mercury porosimeter and the porosity (%v/v) was calculated from the mercury intrusion volume and the true density data.

SUMMARY OF RESULTS

The bulk and tap density values for the various sieve cuts of the control and porous (1.76% w/w effervescent mixture) granules are tabulated below.

Sieve Cut	Bulk Density (g/cc)		Tap Density (g/cc)	
	Control	Porous	Control	Porous
-16+20	0.44	0.42	0.46	0.45
-20+40	0.48	0.45	0.50	0.48
-40+60	0.53	0.49	0.55	0.53
-60+80	0.54	0.52	0.59	0.57

The above bulk and tap density data indicate that for each sieve cut the porous granules had lower density values than the control samples. This trend was also observed for the batches made using different levels of the effervescent mixture.

The total mercury intrusion volume and the percent porosity for the +16, -16+20, and -40+60 sieve cuts of the control and porous (1.76% w/w effervescent mixture) granules are tabulated below.

Sieve Cut	Intrusion Volume (cc/g)		Percent Porosity (% v/v)	
	Control	Porous	Control	Porous
+16	0.27	0.39	28.4	36.1
-16+20	0.26	0.36	27.7	34.3
-40+60	0.21	0.25	23.6	26.6

The percent porosity values for all three sieve cuts of the porous granules were higher than the control granules.

The total mercury intrusion volume and the percent porosity for the -40+60 sieve cut of the control and porous granules prepared using dispersions of HPMC in deionized water and isopropanol as the granulating liquid are shown below.

	Intrusion Volume (cc/g)		Percent Porosity (% v/v)	
	Control	Porous	Control	Porous
HPMC/Water	0.27	0.33	28.4	32.4
HPMC/ Isopropanol	0.39	0.40	35.2	36.7

The above results indicate that the granule porosity increased when the HPMC dispersion in water was used as the granulating liquid. Although the granule porosity was higher for both the control and porous granules for the granulations prepared using the HPMC dispersion in isopropanol, there was no marked difference between the control and the porous granules. This would be expected since water is needed for the effervescent reaction.

The mercury intrusion volume and the percent porosity for the -40+60 sieve cut of the control and porous granules prepared using room temperature and refrigerated powder blends are shown below.

	Intrusion Volume (cc/g)		Percent Porosity (% v/v)	
	Control	Porous	Control	Porous
Room temperature	0.21	0.26	23.6	27.4
Refrigerated	0.21	0.25	23.6	26.6

The above results indicate that refrigerating the powder blend prior to granulation did not increase the granule porosity to any greater extent than the granules prepared using the room temperature powder blend.

The following examples are illustrative of the method of preparing superior tasting, pharmaceutical compositions having porous particles according to the disclosed invention.

EXAMPLE 1

STEP 1

First, 11.4 g sodium bicarbonate and 8.6 g anhydrous citric acid, are combined and then compressed into 1 g compacts using a Carver press applying 4540 kg (10,000 pounds) of force. The compacts are stored in a desiccator overnight. The compacts are then milled by the following procedure:

(a) milling the compacts for 10 seconds;

(b) allowing the mill to cool for 10 seconds; and

(c) milling for another 10 seconds.

The milled powder is then stored in a desiccator overnight.

STEP 2

Calcium carbonate (671.6 g) and pregelatinized starch (75.0 g) are passed through a 20 mesh screen and then placed in a small Lodige mixer. The milled sodium bicarbonate/citric acid powder (3.4 g) is then added to the high shear mixer and the mixture is mixed for 2 minutes. Simple syrup (120 ml) is added while mixing and the mixing is continued for a period of one minute and thirty seconds. The mixer sides are scraped and the mixture is mixed for an additional 30 seconds. The wet granulation is then passed through a 10 mesh screen. The granulation is tray dried in an oven at 54°C (130°F) for six hours and then compressed into 558 mg tablets on a hydraulic press.

EXAMPLE 2

Magaldrate (667.5 g) and Starch 1500 (75.0 g) are passed through a 20 mesh screen and added to a small high shear mixer. Milled sodium bicarbonate/citric acid powder (7.5 g), prepared as above in Example 1, Step 1, is added to the mixer. The magaldrate, Starch 1500, and sodium bicarbonate/citric acid milled powder is mixed for 2 minutes and 360 ml of simple syrup is added while mixing for 4 minutes and 15 seconds. The wet granulation is passed through a 10 mesh screen. The granulation is tray dried in an oven at 54°C (130°F) for six hours and then dried for another 4 hours at 77°C (170°F). The granulation is then milled using a comil, lubricated and flavored and then compressed into 2 g tablets on an hydraulic press.

Claims

1. A method of preparing a superior tasting, pharmaceutical composition of porous particles comprising:
   (a) mixing approximately stoichiometric amounts of an appropriate base and an appropriate acid in a press to produce a compact;
   (b) milling the compact to form an approximately evenly distributed effervescent mixture of the appropriate acid and the appropriate base;

(c) adding the effervescent mixture to a preparation of a pharmacologically active agent to form an active mixture;
(d) granulating the active mixture in admixture with an appropriate amount of a granulating ag nt wherein the granulating agent in combination with said active mixture forms a wet granulation containing water;
(e) drying said wet granulation with applied heat whereby the applied heat and the water in the wet granulation cause the appropriate acid and the appropriate base to react releasing gas from the wet granulation to form porous particles;
(f) milling said porous particles to form a powder, which can be compressed to form a tablet, used in a reconstitutable powder dosage form or filled in a capsule as a quick dissolving powder.

2. A method of preparing a superior tasting, pharmaceutical composition of porous particles comprising:
(a) separately milling approximately stoichiometric amounts of an appropriate acid and an appropriate base to form a milled acid and a milled base;
(b) mixing the milled acid and the milled base to form an effervescent mixture;
(c) adding the effervescent mixture to a preparation of a pharmacologically active agent to form an active mixture;
(d) granulating the active mixture in admixture with an appropriate amount of a granulating agent wherein the granulating agent in combination with said active mixture forms a wet granulation containing water;
(e) drying said wet granulation with applied heat whereby the applied heat and the water in the wet granulation cause the appropriate acid and the appropriate base to react releasing gas from the wet granulation to form porous particles;
(f) milling said porous particles to form a powder, which can be compressed to form a tablet, used in a reconstitutable powder dosage form or filled in a capsule as a quick dissolving powder.

3. A method of preparing a superior tasting, pharmaceutical composition of porous particles comprising:
(a) mixing approximately stoichiometric amounts of an appropriate acid and an appropriate base to form a mixture of the appropriate acid and the appropriate base;
(b) granulating the mixture of the appropriate acid and the appropriate base with an appropriate amount of a non-aqueous granulating liquid containing a binding agent dissolved in absolute alcohol to produce a wet granulation;
(c) drying the wet granulation to form granules of the mixture of the appropriate acid and the appropriate base;
(d) milling the granules of the mixture of the appropriate acid and the appropriate base to form an effervescent mixture of fine particle size;
(e) adding the effervescent mixture of fine particle size to a preparation of a pharmacologically active agent to form an active mixture;
(f) granulating the active mixture in admixture with an appropriate amount of a granulating agent wherein the granulating agent in combination with the active mixture forms a wet granulation containing water;
(g) drying said wet granulation with applied heat whereby the applied heat and the water cause the appropriate acid and the appropriate base to react releasing gas from the wet granulation to form porous particles;
(h) milling said porous particles to form a powder, which can be compressed to form a tablet, used in a reconstitutable powder dosage form, or filled in a capsule as a quick dissolving powder.

4. A method of producing a superior tasting, pharmaceutical composition of porous particles according to claims 1-3 wherein the appropriate acid is selected from the group consisting of citric acid, tartaric acid, malic acid or maleic acid and the appropriate base is selected from the group consisting of sodium carbonate, sodium bicarbonate, potassium carbonate and potassium bicarbonate.

5. A superior tasting, pharmaceutical composition of porous particles produced according to th method of any of claims 1-4.

6. A superior tasting, pharmaceutical composition of porous particles according to claim 5 wherein the pharmacologically active agent is an antacid.

7. A superior tasting, pharmaceutical composition of porous particles according to claim 6 wherein the antacid is selected from the group consisting of aluminum hydroxide, magnesium hydroxide or a combination thereof.

8. A superior tasting, pharmaceutical composition of porous particles according to claim 5 wherein the pharmaceutically active agent is calcium carbonate.

9. A quick dissolving, reconstitutable pharmaceutical composition of porous particles prepared according to claim 1 wherein the pharmaceutically active agent is selected from the group consisting of methylcellulose or hydroxypropylmethylcellulose.

10. A pharmaceutical composition preparable according to any one of claims 1, 2 or 3 wherein the porous particles are produced by an effervescent mixture of an appropriate acid and an appropriate base.

11. A pharmaceutical composition according to claim 10 wherein the appropriate acid is selected from the group consisting of citric acid, tartaric acid, malic acid or maleic acid and the appropriate base is selected from the group consisting of sodium carbonate, sodium bicarbonate, potassium carbonate and potassium bicarbonate.

12. A pharmaceutical composition according to claim 10 or 11 wherein the pharmacologically active agent is an antacid.

13. A pharmaceutical composition according to claim 12 wherein the antacid is selected from the group consisting essentially of aluminum hydroxide, magnesium hydroxide or a combination thereof.

Patentansprüche

1. Verfahren zur Herstellung eines Arzneimittels mit verbessertem Geschmack aus porösen Partikeln, umfassend:
   (a) Vermischen etwa stöchiometrischer Mengen einer geeigneten Base und einer geeigneten Säure in einer Presse zur Herstellung eines Preßlings,
   (b) Vermahlen des Preßlings zur Erzeugung eines in etwa gleichmäßig verteilten Schäumungsmittelgemischs der geeigneten Säure und der geeigneten Base,
   (c) Zugeben des Schäumungsmittelgemischs zur Präparation eines pharmakologisch wirksamen Wirkstoffs zur Erzeugung eines wirksamen Gemischs,
   (d) Granulieren des wirksamen Gemischs zusammen mit einer geeigneten Menge eines Granulierungsmittels, wobei das Granulierungsmittel in Kombination mit dem wirksamen Gemisch ein feuchtes, Wasser enthaltendes Granulat bildet,
   (e) Trocknen des feuchten Granulats durch zugeführte Hitze, wobei durch die zugeführte Hitze und das Wasser in dem feuchten Granulat eine Umsetzung der geeigneten Säure und der geeigneten Base bewirkt wird, wobei aus dem feuchten Granulat unter Bildung poröser Partikel Gas freigesetzt wird,
   (f) Vermahlen der porösen Partikel zu einem Pulver, das zu einer Tablette komprimiert werden kann, die in einer rekonstituierbaren Pulverdosierungsform verwendet oder als ein sich schnell auflösendes Pulver in eine Kapsel gefüllt wird.

2. Verfahren zur Herstellung eines Arzneimittels mit verbessertem Geschmack aus porösen Partikeln, umfassend:
   (a) getrenntes Vermahlen etwa stöchiometrischer Mengen einer geeigneten Säure und einer geeigneten Base zum Erhalt einer gemahlenen Säure und einer gemahlenen Base,
   (b) Vermischen der gemahlenen Säure und der gemahlenen Base zur Erzeugung eines Schäumungsmittelgemischs,
   (c) Zug ben des Schäumungsmittelgemischs zu iner Präparation ines pharmakologisch wirksamen Wirkstoffs zur Erzeugung eines wirksamen Gemischs,
   (d) Granulieren des wirksamen Gemischs zusammen mit einer geeigneten Menge eines Granuli - rungsmittels, wobei das Granulierungsmittel in Kombination mit dem wirksamen Gemisch ein feuchtes, Wasser enthaltendes Granulat bildet,

(e) Trocknen des feuchten Granulats mit zugeführter Hitze, wobei durch die zugeführte Hitze und das Wasser in dem feuchten Granulat eine Umsetzung der geeigneten Säure und der geeigneten Base bewirkt wird, wobei Gas aus dem feuchten Granulat unter Bildung poröser Partikel freigesetzt wird,

(f) Vermahlen der porösen Partikel zu einem Pulver, das zu einer Tablette komprimiert werden kann, die in einer rekonstituierbaren Pulverdosierungsform verwendet oder als ein sich schnell auflösendes Pulver in eine Kapsel gefüllt wird.

3. Verfahren zur Herstellung eines Arzneimittels mit verbessertem Geschmack aus porösem Partikeln, umfassend:

(a) Vermischen etwa stöchiometrischer Mengen einer geeigneten Säure und einer geeigneten Base zur Erzeugung eines Gemischs der geeigneten Säure und der geeigneten Base,

(b) Granulieren des Gemischs aus der geeigneten Säure und der geeigneten Base mit einer geeigneten Menge einer nicht-wäßrigen Granulierungsflüssigkeit, die ein in absolutem Alkohol gelöstes Bindemittel enthält, zur Herstellung eines feuchten Granulats,

(c) Trocknen des feuchten Granulats zur Erzeugung von Körnchen aus dem Gemisch der geeigneten Säure und der geeigneten Base,

(d) Vermahlen der Körnchen aus dem Gemisch der geeigneten Säure und der geeigneten Base zur Erzeugung eines Schäumungsmittelgemischs mit einer geringen Partikelgröße,

(e) Zugeben des Schäumungsmittelgemischs mit einer geringen Partikelgröße zu einer Präparation eines pharmakologisch wirksamen Wirkstoffs zur Erzeugung eines wirksamen Gemischs,

(f) Granulieren des wirksamen Gemischs zusammen mit einer geeigneten Menge eines Granulierungsmittels, wobei das Granulierungsmittel in Kombination mit dem wirksamen Gemisch ein feuchtes, Wasser enthaltendes Granulat bildet,

(g) Trocknen des feuchten Granulats durch zugeführte Hitze, wobei durch die zugeführte Hitze und das Wasser eine Umsetzung der geeigneten Säure und der geeigneten Base bewirkt wird, wobei Gas aus dem feuchten Granulat unter Bildung poröser Partikel freigesetzt wird,

(h) Vermahlen der porösen Partikel zu einem Pulver, das zu einer Tablette komprimiert werden kann, die in einer rekonstituierbaren Pulverdosierungsform verwendet oder als ein sich schnell auflösendes Pulver in eine Kapsel gefüllt wird.

4. Verfahren zur Herstellung eines Arzneimittels mit verbessertem Geschmack aus porösen Partikeln nach einem der Ansprüche 1 bis 3, wobei die geeignete Säure Citronensäure, Weinsäure, Äpfelsäure oder Maleinsäure und die geeignete Base Natriumcarbonat, Natriumbicarbonat, Kaliumcarbonat oder Kaliumbicarbonat ist.

5. Arzneimittel mit verbessertem Geschmack aus porösen Partikeln, hergestellt gemäß dem Verfahren nach einem der Ansprüche 1 bis 4.

6. Arzneimittel mit verbessertem Geschmack aus porösen Partikeln nach Anspruch 5, wobei der pharmakologisch wirksame Wirkstoff ein Antacidum ist.

7. Arzneimittel mit verbessertem Geschmack aus porösen Partikeln nach Anspruch 6, wobei das Antacidum Aluminiumhydroxid, Magnesiumhydroxid oder eine Kombination davon ist.

8. Arzneimittel mit verbessertem Geschmack aus porösen Partikeln nach Anspruch 5, wobei der pharmakologisch wirksame Wirkstoff Calciumcarbonat ist.

9. Sich schnell auflösendes, rekonstituierbares Arzneimittel aus porösen Partikeln, hergestellt nach Anspruch 1, wobei der pharmazeutisch wirksame Wirkstoff Methylcellulose oder Hydroxypropylmethylcellulose ist.

10. Arneimittel, erhältlich nach einem der Ansprüche 1, 2 oder 3, wobei die porösen Partikel durch ein Schäumungsmittelgemisch aus einer geeigneten Säure und einer geeigneten Base hergestellt werden.

11. Arzneimittel nach Anspruch 10, wobei die geeignete Säure Citronensäure, Weinsäure, Äpfelsäure oder Maleinsäure und die geeignete Base Natriumcarbonat, Natriumbicarbonat, Kaliumcarbonat oder Kaliumbicarbonat ist.

12. Arzneimittel nach Anspruch 10 oder 11, wobei der pharmakologisch wirksame Wirkstoff ein Antacidum ist.

13. Arzneimittel nach Anspruch 12, wobei das Antacidum ausgewählt ist aus der Gruppe, die im w sentlichen aus Aluminiumhydroxid, Magnesiumhydroxid und einer Kombination davon besteht.

Revendications

1. Procédé de préparation d'une composition pharmaceutique à saveur améliorée de particules poreuses comprenant :
   (a) le mélange de quantités approximativement stoechiométriques d'une base appropriée et d'un acide approprié dans une presse pour produire un produit compact,
   (b) le broyage du produit compact pour former un mélange effervescent approximativement uniformément distribué de l'acide approprié et de la base appropriée,
   (c) l'addition du mélange effervescent à une préparation d'un agent pharmacologiquement actif pour former un mélange actif,
   (d) la granulation du mélange actif en mélange avec une quantité appropriée d'un agent de granulation, dans laquelle l'agent de granulation en association avec ledit mélange actif forme une granulation mouillée contenant de l'eau,
   (e) le séchage de ladite granulation mouillée en appliquant de la chaleur, la chaleur appliquée et l'eau dans la granulation mouillée provoquant de ce fait une réaction de l'acide approprié et de la base appropriée en libérant un gaz à partir de la granulation mouillée pour former des particules poreuses,
   (f) le broyage desdites particules poreuses pour former une poudre, laquelle peut être compressée pour former un comprimé, utilisée dans une présentation en poudre reconstituable ou introduite dans une capsule sous la forme d'une poudre se dissolvant rapidement.

2. Procédé de préparation d'une composition pharmaceutique à saveur améliorée de particules poreuses comprenant :
   (a) le broyage séparé de quantité approximativement stoechiométriques d'un acide approprié et d'une base appropriée pour former un acide broyé et une base broyée,
   (b) le mélange de l'acide broyé et de la base broyée pour former un mélange effervescent,
   (c) l'addition du mélange effervescent à une préparation d'un agent pharmacologiquement actif pour former un mélange actif,
   (d) la granulation du mélange actif en mélange avec une quantité appropriée d'un agent de granulation, dans laquelle l'agent de granulation en association avec ledit mélange actif forme une granulation mouillée contenant de l'eau,
   (e) le séchage de ladite granulation mouillée en appliquant de la chaleur, la chaleur appliquée et l'eau dans la granulation mouillée provoquant de ce fait une réaction de l'acide approprié et de la base appropriée en libérant un gaz à partir de la granulation mouillée pour former des particules poreuses,
   (f) le broyage desdites particules poreuses pour former une poudre, laquelle peut être compressée pour former un comprimé, utilisée dans une présentation de poudre reconstituable ou introduite dans une capsule sous la forme d'une poudre se dissolvant rapidement.

3. Procédé de préparation d'une composition pharmaceutique à saveur améliorée de particules poreuses comprenant :
   (a) le mélange de quantités approximativement stoechiométriques d'un acide approprié et d'une base appropriée pour former un mélange de l'acide approprié et de la base appropriée,
   (b) la granulation du mélange de l'acide approprié et de la base appropriée avec une quantité appropriée d'un liquide non aqueux de granulation contenant un liant dissous dans de l'alcool absolu pour produire une granulation mouillée,
   (c) l séchage de la granulation mouillé pour former d s granules du mélange de l'acide approprié et de la base appropriée,
   (d) le broyage des granules du mélange de l'acide approprié et de la base appropriée pour former un mélange effervescent de dimension de fines particules,
   (e) l'addition du mélange effervescent de dimension de fines particul s à une préparation d'un agent pharmacologiquement actif pour form r un mélange actif,

(f) la granulation du mélange actif en mélange avec une quantité appropriée d'un agent de granulation, dans laquelle l'agent de granulation en association avec le mélange actif forme une granulation mouillée contenant de l'eau,
(g) le séchage de ladite granulation mouillée en appliquant de la chaleur, la chaleur appliquée et l'eau provoquant de ce fait une réaction de l'acide approprié et de la base appropriée en libérant un gaz à partir de la granulation mouillée pour former des particules poreuses,
(h) le broyage desdites particules poreuses pour former une poudre, laquelle peut être compressée pour former un comprimé, utilisée dans une présentation de poudre reconstituable ou introduite dans une capsule sous la forme d'une poudre se dissolvant rapidement.

4. Procédé de production d'une composition pharmaceutique à saveur améliorée de particules poreuses selon les revendications 1 à 3, dans lequel on choisit l'acide approprié dans le groupe constitué de l'acide citrique, de l'acide tartrique, de l'acide malique, de l'acide maléique et on choisit la base appropriée dans le groupe constitué du carbonate de sodium, du bicarbonate de sodium, du carbonate de potassium et du bicarbonate de potassium.

5. Composition pharmaceutique à saveur améliorée de particules poreuses produite selon le procédé selon l'une quelconque des revendications 1 à 4.

6. Composition pharmaceutique à saveur améliorée de particules poreuses selon la revendication 5, dans laquelle l'agent pharmacologiquement actif est un antiacide.

7. Composition pharmaceutique à saveur améliorée de particules poreuses selon la revendication 6, dans laquelle on choisit l'antiacide dans le groupe constitué de l'hydroxyde d'aluminium, de l'hydroxyde de magnésium ou de l'une de leurs associations.

8. Composition pharmaceutique à saveur améliorée de particules poreuses selon la revendication 5, dans laquelle l'agent pharmacologiquement actif est le carbonate de calcium.

9. Composition pharmaceutique de particules poreuses, reconstituable, se dissolvant rapidement, préparée selon la revendication 1, dans laquelle on choisit l'agent pharmacologiquement actif dans le groupe constitué de la méthylcellulose ou de l'hydroxypropylméthylcellulose.

10. Composition pharmaceutique pouvant être préparée selon l'une quelconque des revendications 1, 2 ou 3, dans laquelle on produit les particules poreuses par un mélange effervescent d'un acide approprié et d'une base appropriée.

11. Composition pharmaceutique selon la revendication 10, dans laquelle on choisit l'acide approprié dans le groupe constitué de l'acide citrique, de l'acide tartrique, de l'acide malique ou de l'acide maléique et on choisit la base appropriée dans le groupe constitué du carbonate de sodium, du bicarbonate de sodium, du carbonate de potassium et du bicarbonate de potassium.

12. Composition pharmaceutique selon la revendication 10 ou 11, dans laquelle l'agent pharmacologiquement actif est un antiacide.

13. Composition pharmaceutique selon la revendication 12, dans laquelle on choisit l'antiacide dans le groupe constitué essentiellement de l'hydroxyde d'aluminium, de l'hydroxyde de magnésium ou de l'une de leurs associations.